

IN THE CLAIMS:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1-21. (canceled)

22. (currently amended): A method of inserting a heterologous gene coding sequence into an endogenous gene in a mouse embryonic stem cell genome and expressing said heterologous gene coding sequence, comprising the step of transforming the mouse embryonic stem cell with a random gene trap vector comprising a DNA construct, wherein the heterologous gene coding sequence lacks a promoter, and (ii) comprises the sequence:

5' X-A-P-B-Q-C-Y 3'

in which

X and Y are separately, DNA sequences substantially homologous with a host gene locus;

P is an internal ribosome entry site (IRES);

Q is the heterologous gene sequence, including a translation start codon; and

A, B, and C are, separately, optional linker sequence[s];

wherein the DNA construct further comprises a polyadenylation signal at the 3' (downstream) end of Q and a splice acceptor site located 5' (upstream) of Q.

23. (Original): A method according to Claim 22 where the heterologous gene coding sequence is randomly inserted into an endogenous gene so that transcription of the heterologous gene coding sequence is directed by the host regulatory elements of the endogenous gene.

24. (Original): A method according to Claim 22 in which the splice acceptor permits functional integration of the heterologous gene coding sequence into an intron sequence.

25. (Previously Canceled)
26. (Original): A method according to Claim 22 further comprising the step of identifying cells expressing the heterologous gene coding sequence.
27. (Previously Amended): A method according to Claim 26 wherein the construct also comprises a gene encoding a selectable marker and the method comprises selecting cells that express the selectable marker.
28. (Previously Amended): A mouse embryonic stem cell comprising a heterologous gene code sequence inserted by the method of Claim 22.
29. (Previously Amended): A descendant of the mouse embryonic stem cell according to Claim 28, wherein the descendant has inherited the inserted heterologous gene coding sequence.
30. (Withdrawn): An animal comprising a heterologous gene coding sequence inserted by the method of Claim 22.
31. (Withdrawn): A descendant of an animal according to Claim 30, wherein the descendant has inherited the inserted heterologous gene coding sequence.
32. (Currently Amended): A DNA construct for randomly inserting a heterologous gene sequence into a mouse cell genome, said heterologous gene sequence lacking a promoter and comprising the sequence:
- 5' X-A-P-B-Q-C-Y 3'
- in which
- X and Y are separately, DNA sequences substantially homologous with a

- host gene locus;
- P is an internal ribosome entry site (IRES);
- Q is the heterologous gene sequence, including a translation start codon; and
- A, B and C are, separately, optional linker sequence[s];

wherein the DNA construct further comprises a polyadenylation signal at the 3' (downstream) end of Q and a splice acceptor site located 5' (upstream) of Q.

33. (Original): A DNA construct according to Claim 32 in which the splice acceptor permits functional integration of the heterologous gene into an intron sequence.

34. (Previously Amended): A DNA construct according to Claim 32 in which the construct also comprises a gene encoding a selectable marker to facilitate selection of mouse cells containing a heterologous gene that has been inserted into an endogenous gene.

35-40. (Previously Canceled)

41. (Previously Amended): A method according to Claim 22 wherein the construct also comprises a gene encoding antibiotic resistance, and the method comprises selecting cells that express the antibiotic resistance.

42. (Previously Amended): A DNA construct according to Claim 32 wherein the construct additionally comprises a gene encoding antibiotic resistance.

43-46. (Previously Canceled)

47-53. (Canceled)

54. (Withdrawn): A mouse comprising a cell according to Claim 53.

55. (Withdrawn): A descendant of a mouse according to Claim 54, wherein the

descendant has inherited the inserted heterologous gene coding sequence.

56-60. (Canceled)

61. (Withdrawn): A mouse comprising a heterologous gene coding sequence inserted by the method of claim 22.

62. (Withdrawn): A descendant of the mouse according to Claim 61, wherein the descendant has inherited the inserted heterologous gene coding sequence.

63. (Withdrawn): A cell comprising a heterologous gene coding sequence inserted according to the method of Claim 56.

64. (Withdrawn): A descendant of the cell according to Claim 63, wherein the descendant has inherited the inserted heterologous gene coding sequence.

65. (Withdrawn): A mouse comprising a heterologous gene coding sequence inserted according to the method of Claim 56.

66. (Withdrawn): A descendant of the mouse according to Claim 65, wherein the descendant has inherited the inserted heterologous gene coding sequence.

67. (Withdrawn): A cell comprising an inserted heterologous gene coding sequence inserted into a target endogenous gene in a eukaryotic cellular host cell genome by transforming the host cell with a vector comprising a DNA construct, wherein the DNA construct comprises the elements:

5' X-A-P-B-Q-C-Y 3'

in which

X and Y are substantially homologous with separate sequences from the target endogenous gene and are of sufficient length to undergo homologous recombination with the host cell genome so as to insert the A-P-B-Q-C elements into the host cell genome;

P is an internal ribosome entry site (IRES);

Q is the heterologous gene coding sequence; and

A, B, and C are, separately, linker sequence or a covalent bond.

68. (Withdrawn): A descendant of the cell of Claim 67, wherein the descendant has inherited the inserted heterologous gene coding sequence.

69. (Withdrawn): A mouse comprising an inserted heterologous gene coding sequence inserted into a target endogenous gene in a eukaryotic cellular host cell genome by transforming the host cell with a vector comprising a DNA construct, wherein the DNA construct comprises the elements:

5' X-A-P-B-Q-C-Y 3'

in which

X and Y are substantially homologous with separate sequences from the target endogenous gene and are of sufficient length to undergo homologous recombination with the host cell genome so as to insert the A-P-B-Q-C elements in to the host cell genome;

P is an internal ribosome entry site (IRES);

Q is the heterologous gene coding sequence; and

A, B, and C are, separately, linker sequence or a covalent bond.

70. (Withdrawn): A descendant of the mouse of Claim 69, wherein the descendant has inherited the inserted heterologous gene coding sequence.

71. (Withdrawn): A cell according to Claim 67, wherein the construct also comprises a gene encoding a selectable marker.

72. (Withdrawn): A mouse according to Claim 69, wherein the construct also comprises a gene encoding a selectable marker.

73. (Previously Presented): A DNA construct for inserting a heterologous gene coding sequence into a target endogenous gene in a eukaryotic cellular host cell genome, wherein the construct comprises the elements:

5' X-A-P-B-Q-C-Y 3'

in which

X and Y are substantially homologous with separate sequences from the target endogenous gene and are of sufficient length to undergo homologous recombination with the host cell genome so as to insert the A-P-B-Q-C elements into the host cell genome;

P is an internal ribosome entry site (IRES);

Q is the heterologous gene coding sequence; and

A, B, and C are, separately, linker sequence or a covalent bond.

74. (Previously Presented): The DNA construct according to Claim 73, wherein the construct also comprises a gene encoding a selectable marker.